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1.	TITLE-ABSTR-KEY(anti-oxidant) and TITLE-ABSTR-KEY(diseases) [All Sources(- All Sciences -)]	735

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Antioxidant vitamins may help transplant patients

CORVALLIS, Ore. – A new clinical study just published in the medical journal *Lancet* suggests that people who receive heart transplants, and possibly some other types of transplants or medical procedures, may get important health benefits by taking supplements of both vitamins C and E.

Patients who received supplements of these two antioxidant vitamins had very little coronary arteriosclerosis associated with their transplants. Ordinarily, this is one of the most important limitations to the long-term survival of cardiac transplant recipients - their arteries tend to thicken and clog unusually fast after a transplant, and this disease is present in over 70 percent of recipients within three years.

The research was done by scientists in the Linus Pauling Institute at Oregon State University and the Cardiovascular Division of Brigham and Women's Hospital in Boston.

Oxidant stress tends to contribute to accelerated coronary arteriosclerosis following a transplant, and the body's natural antioxidant defenses are often reduced. Treatment with antioxidant vitamins appears to have significant value in addressing this problem, the study found.

"Arteriosclerosis is a health condition that's a problem for many people, but it is much more acute and occurs more rapidly in people who have had heart transplants," said Balz Frei, professor and director of the Linus Pauling Institute, and co-author on the study.

This double-blind study was done with 40 heart transplant patients. Half of them received 1000 milligrams of vitamin C and 800 international units of vitamin E each day. The others received a placebo.

After one year, the study showed that coronary arteries had significantly thickened and narrowed in the group that received a placebo, but were largely unchanged in those who received the antioxidants. The use of antioxidants did not appear to interfere with the immunosuppressive drugs the patients needed to take, or cause any increase in transplant rejection.

Some past studies looking at this and other issues had used vitamin E, by itself, as a supplement, and failed to improve patients' outcomes, the study said. The use of both vitamins C and E in combination appears to work much better, as there may be complementary interactions between the two vitamins which give results different than either one of them would if used separately.

This type of antioxidant therapy may also have value in other types of organ transplants, such as kidney, lung and liver, Frei said, or such medical procedures as angioplasty. Angioplasty is a common medical procedure for patients with coronary artery disease, but one that often has to be repeated within a few months when arteries once again become narrowed.

By David Stauth, 541-737-0787
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Oxidant-protease interaction in the lung. Prospects for antioxidant therapy

R Buhl, A Meyer and C Vogelmeier
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A M E R I C A N C O L L E G E O F
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Oxidant-Protease Interaction in the Lung*

Prospects for Antioxidant Therapy

Roland Buhl, MD; Andreas Meyer, MD; and Claus Vogelmeier, MD

In inflammatory lung disorders, oxidants and proteases complement each other in their potential to destroy lung parenchyma. It is therefore rational to combine therapeutic strategies aimed at augmenting the antiproteolytic defenses of the lung in diseases such as emphysema with antioxidant strategies. In the healthy lung, the oxidant burden is balanced by the local antioxidant defenses. However, both an increased oxidant burden and/or decreased antioxidant defenses may reverse the physiologic oxidant-antioxidant balance in favor of oxidants, leading to lung injury. This concept points to an obvious therapeutic strategy: augmentation of the antioxidant screen of the lung to prevent oxidant-mediated tissue damage. Studies using reduced glutathione (GSH), the major pulmonary antioxidant, as a model therapeutic agent demonstrated that GSH can be administered directly to the respiratory epithelial surface by aerosol and is fully functional as an antioxidant both *in vitro* and *in vivo*. In pulmonary diseases such as idiopathic pulmonary fibrosis or following HIV infection, GSH aerosol therapy not only normalized deficient pretherapy GSH levels in the lung, but was capable of favorably influencing cellular events such as oxidant release by pulmonary inflammatory cells. The same was true for oral antioxidant therapy with N-acetylcysteine, a glutathione precursor. These results suggest that it is possible to use antioxidants to reverse the imbalance between oxidants and antioxidants at the site of oxidant injury to prevent the progressive tissue damage in lung disorders characterized by high oxidant states. Antioxidants, alone and in combination with antiproteases, merit further long-term studies for clinical therapy.

(CHEST 1996; 110:267S-272S)

Key words: α_1 -antitrypsin; antioxidants; emphysema; oxidants; proteases

In inflammatory lung disorders, oxidants and proteases complement each other in the potential to destroy lung parenchyma.¹⁻⁷ Proteases are enzymes able to attack and degrade proteins by cleavage of peptide bonds in the protein chain. The major source of proteases are inflammatory cells attracted to the lung as part of the host defense.^{1-3,5,6,8,9} Normally, the lung is adequately protected against proteases by antiproteases, molecules that rapidly bind to proteases, thereby irreversibly inhibiting their proteolytic activity. α_1 -Antitrypsin (α_1 -AT), secretory leukoprotease inhibitor (SLPI), and α_2 -macroglobulin are antiproteases central to the pulmonary antiproteolytic defenses.^{1,3,6,10-12} Various acute and chronic inflammatory lung diseases are characterized by an imbalance between proteases and antiproteases in the lower respiratory tract, among them pulmonary emphysema,

cystic fibrosis, ARDS, and acute and chronic bronchitis.^{1,3,5,6,10,11,13-15} With regard to emphysema, if the antiproteolytic protective screen of the lower respiratory tract is insufficient, unregulated proteolytic enzymes such as neutrophil elastase released by inflammatory cells are able to digest connective-tissue proteins, eventually leading to the enlarged terminal airspaces typical for the disease. The antiproteolytic shield may be compromised either due to an absolute deficiency of α_1 -AT, the major pulmonary antiprotease, or due to a local imbalance between proteases and antiproteases secondary to a functional antiproteolytic deficiency. α_1 -AT deficiency is an autosomal-recessive disorder associated with markedly reduced α_1 -AT plasma levels. Circumstances leading to a functional antiproteolytic deficiency include cigarette smoking or recurrent bacterial infections.^{1-3,5,6,10,13,14,16,17}

Oxidants play a key role in these pathogenic processes. Oxidants or free radicals are atoms or molecules capable of independent existence that contain one or more unpaired electrons, making these species highly reactive.^{2,4,7,18} Major sources of oxidants in the lower respiratory tract are activated phagocytic cells or inhaled cigarette smoke. Cigarette smoking alone creates an enormous oxidant burden on the airway

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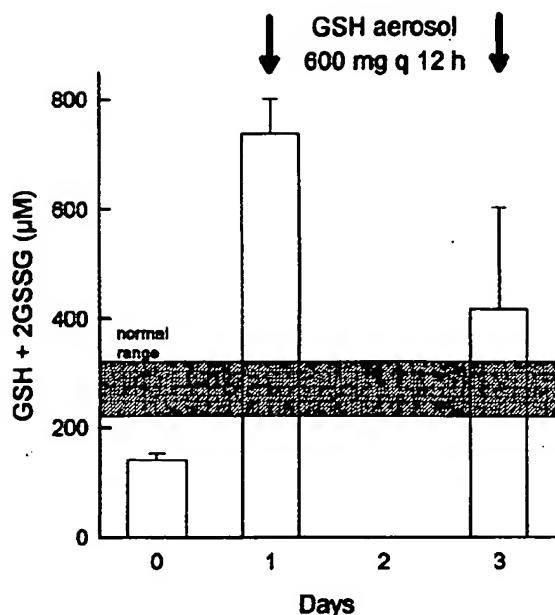


FIGURE 1. Concentrations of total glutathione (GSH+2GSSG) in lung ELF of patients with IPF treated with GSH by aerosol (adapted from Borok et al³⁸).

epithelial surface with an estimated 10^{14} to 10^{16} free radicals per puff. In addition, cigarette smoking is associated with the recruitment and activation of macrophages and neutrophils to the lung, leading to chronic, low-level inflammation of the lower respiratory tract.^{4,7,19,20} Oxidants can cause injury and cell death by modifying and/or disturbing the structure and function of any cellular or noncellular component. In the extracellular milieu, oxidants can effectively inactivate molecules required to maintain the integrity of the pulmonary tissue, *e.g.*, antiproteases such as α_1 -AT. The active center of α_1 -AT contains a methionine residue that can be easily oxidized *in vitro* both by strong oxidants and by oxidants generated and released by phagocytic cells.^{2,4,16-20} Consequently, when analyzed in fluid obtained by BAL from the lower respiratory tract of cigarette smokers, α_1 -AT is partly inactivated due to oxidation, leading to insufficient inhibition of neutrophil elastase. Other major pulmonary antiproteases such as SLPI can be inactivated by cell-derived or inhaled oxidants in a similar way.^{11,16,19,20}

Importantly, while both oxidants and proteases can damage lung tissue directly, this damaging effect is potentiated by the fact that oxidants can inactivate antiproteases, and antioxidants can be inactivated by proteases. Thus, it is the intermixing of proteolytic enzymes and oxidants that explains the tissue damage seen in inflammatory lung diseases such as emphysema.^{1-6,10,13,16,17,19,20} With regard to α_1 -AT replacement therapy in patients with emphysema, since α_1 -AT is a major target of oxidant injury, it is

rational to combine this therapeutic strategy with strategies aimed at augmenting the antioxidant protection of the lung to balance the oxidant burden, thereby protecting the infused α_1 -AT once it reaches the lung. The feasibility of this concept is highlighted by *in vitro* studies demonstrating that α_1 -AT can be protected from oxidative inactivation by antioxidants, among them reduced glutathione (GSH) methionine, N-acetylcysteine, a glutathione precursor, ascorbate, and catalase.^{1,3,4,17,21-23}

PULMONARY ANTIOXIDANT DEFENSE MECHANISMS

The potential of oxidants to damage pulmonary tissue is dependent on the local antioxidant defense mechanisms. Antioxidants transform free radicals into less reactive species, thereby limiting their toxic effects. Even when present at low concentrations compared with those of an oxidizable substrate, antioxidants significantly delay or prevent oxidation of that substrate.^{4,24,25} Normally, the respiratory epithelium is adequately protected against oxidants by a variety of intracellular and extracellular antioxidants, including antioxidant enzyme systems and molecules that scavenge free radicals and neutralize the "physiologic" oxidant burden created by both exogenous and endogenous free radicals. The vital importance of antioxidants for cellular integrity and extracellular functions is highlighted by the redundancy of the antioxidative mechanisms and the high concentrations of major antioxidants in the various pulmonary compartments. Among the intracellular antioxidant enzymes are superoxide dismutase (SOD), catalase, and the glutathione redox cycle utilizing the enzymes glutathione reductase and glutathione peroxidase. Among the small nonenzymatic antioxidants are vitamins E, A, and C, and GSH. The extracellular antioxidants present in the fluid lining the epithelium of the lower respiratory tract, the so-called epithelial lining fluid (ELF), also include catalase, SOD, plasma proteins such as albumin, ceruloplasmin, or transferrin, GSH, and vitamins.^{4,24-28}

The dominant small antioxidant molecule both intracellularly and in ELF is GSH. The reduced form of glutathione functions as an efficient intracellular and extracellular antioxidant by scavenging toxic oxygen radicals. Cells are thought to be protected by extracellular GSH from oxidants produced and released by inflammatory cells, and by intracellular GSH from oxidants generated in normal biochemical processes, as well as from xenobiotics.^{4,29-31} In the lung, GSH is present in high concentrations in the ELF of the lower respiratory tract, with normal levels in humans more than 50-fold greater than those in plasma. Furthermore, human ELF is known to contain all elements of

the redox cycle of the GSH system, including glutathione peroxidase and glutathione reductase.^{24-30,32}

GLUTATHIONE AEROSOL THERAPY TO AUGMENT THE ALVEOLAR EPITHELIAL ANTIOXIDANT SCREEN

The ready access of the respiratory epithelial surface by aerosol and by BAL provides opportunities to evaluate and monitor therapeutic strategies directed at reducing the oxidant burden and/or augmenting the antioxidant defense mechanisms in the lower respiratory tract, thereby correcting an oxidant-antioxidant imbalance directly at the site of disease.^{4,7,33,34}

Using glutathione as a model therapeutic agent with antioxidant activity, *in vitro* studies demonstrated that a solution of GSH can be placed in aerosol droplets that are able to reach the lower respiratory tract. The aerosolization process itself did not alter the structure of the glutathione molecule, *i.e.*, the GSH remained reduced.³⁴ Animal studies showed that glutathione administered by aerosol augmented the lung ELF antioxidant screen without adverse effects.³⁴ Thus, functional GSH can be delivered by aerosol to directly augment the ELF GSH levels of the respiratory epithelial surface, an approach that may prove useful in the therapy of various lung disorders.^{4,7,30,34}

The validity of these concepts in humans is highlighted by idiopathic pulmonary fibrosis (IPF) and infection with the HIV. Both diseases are associated in the lung with a severe imbalance between an inflammatory cell-derived oxidant burden and decreased levels of glutathione in the fluid lining the alveolar epithelium.^{4,7,30,32,35-41}

IDIOPATHIC PULMONARY FIBROSIS

IPF is characterized by pulmonary inflammation in response to an as yet unknown stimulus, alveolar epithelial injury, and progressive fibrosis.^{35,37,38,41} The spontaneous release by inflammatory cells in the lung of increased amounts of oxygen radicals that are cytotoxic to epithelial cells is thought to play a significant role in the pathogenesis of the epithelial injury.^{35,37,38} In addition, lung ELF glutathione concentrations in patients with IPF are markedly decreased.^{30,36,38,41} Given the huge inflammatory cell-derived oxidant burden, the GSH deficiency magnifies the oxidant-antioxidant imbalance at the patient's alveolar surface, thus increasing the susceptibility to the severe epithelial cell damage characteristic of IPF. Increased levels of oxidized methionine in BAL fluid proteins from patients with IPF reflect the oxidant burden in the lung.⁴² Therefore, a rational therapeutic strategy for IPF is to augment the alveolar epithelial antioxidant screen. To evaluate this concept, GSH (600 mg) was administered via aerosol twice daily for 3 days to individuals with IPF.³⁸ One hour after the first aerosol,

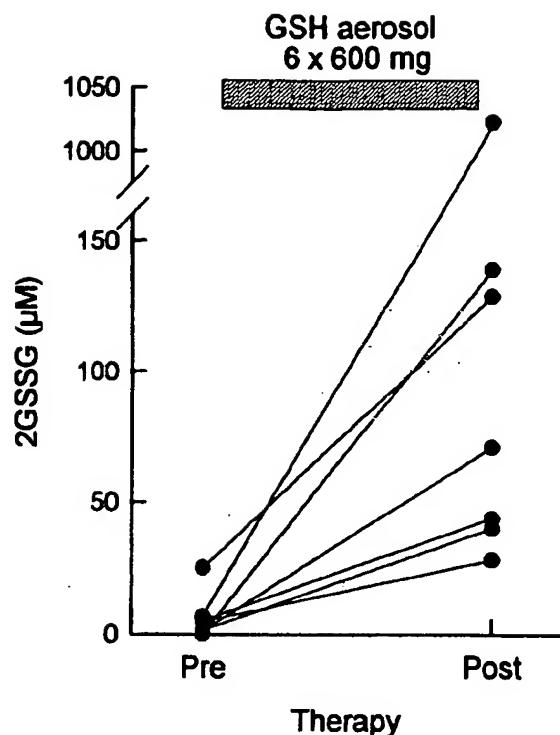


FIGURE 2. Concentrations of oxidized glutathione (2GSSG) in lung ELF of patients with IPF treated with GSH by aerosol (adapted from Borok et al³⁸).

ELF glutathione levels increased significantly compared with deficient pretherapy levels. One hour after the last aerosol, ELF glutathione levels were still higher than pretherapy levels, although not significantly so (Fig 1). A parallel increase in levels of oxidized glutathione in all individuals studied indicated that the aerosolized GSH was being utilized as an antioxidant, since GSH is not oxidized by the aerosolization process (Fig 2). Consistent with this observation, spontaneous lung inflammatory cell superoxide anion release decreased significantly following aerosol therapy (Fig 3).

The same was true when patients with IPF were treated with the glutathione precursor N-acetylcysteine (NAC).⁴¹ Following oral therapy with NAC (600 mg) 3 times daily for 5 days, glutathione levels in fluid obtained by BAL increased significantly compared with pretherapy concentrations, whereas the increase in ELF glutathione levels, although impressive, did not reach significance. This form of therapy was equally well tolerated; all routine clinical and bronchoscopic parameters remained unchanged.

ASYMPTOMATIC INFECTION WITH THE HIV

A severe imbalance between oxidants and antioxidants in the lung may also play a major pathogenic role in infection with the HIV.^{30,32,39,40,43} In asymptomatic HIV-seropositive individuals, the number of inflam-

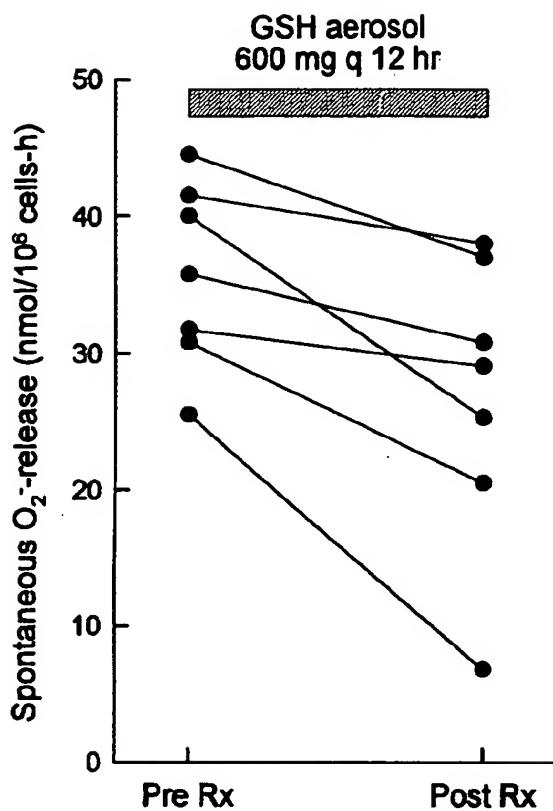


FIGURE 3. Spontaneous release of superoxide anion (O_2^-) by alveolar macrophages of patients with IPF before and after treatment with GSH by aerosol (adapted from Borok et al³⁸).

matory cells recovered by BAL from the lower respiratory tract and the average spontaneous oxidant release by fresh alveolar macrophages were significantly higher than in healthy individuals. The validity of these considerations is illustrated by the fact that the levels of oxidants released by alveolar macrophages of the HIV-seropositive individuals were comparable to the levels of oxidants released by alveolar macrophages of cigarette smokers.³⁹ In addition, lung ELF glutathione concentrations in HIV-infected patients were decreased to about 60% of normal,^{32,43} ie, there is a marked deficiency of antioxidant protective mechanisms in the face of an exaggerated oxidant burden on the alveolar epithelial surface.⁴⁰

In an attempt to reverse this situation, GSH was aerosolized to HIV-infected patients.⁴³ Following 6 twice-daily doses of 600 mg GSH, ELF total glutathione levels increased and remained in the normal range for at least 3 h after therapy (Fig 4). As in IPF patients, the percentage of oxidized glutathione in ELF increased, probably reflecting the utilization of glutathione as an antioxidant *in vivo*.⁴³

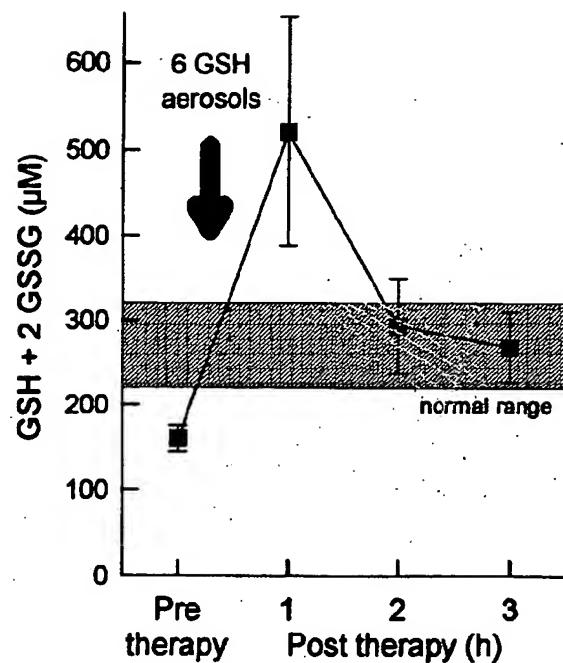


FIGURE 4. Concentrations of total glutathione (GSH+2GSSG) in lung ELF of asymptomatic HIV-infected patients treated with GSH by aerosol (adapted from Holroyd et al⁴³).

FUTURE PROSPECTS OF ANTIOXIDANT THERAPY

These studies demonstrate that it is a feasible and safe therapeutic approach to augment lung glutathione levels in diseases associated with an ELF glutathione deficiency using either GSH or GSH precursors. Antioxidant therapy positively influenced key pathogenic processes both in IPF patients and in HIV-infected individuals without adverse effects. Similar strategies could be beneficial in other pulmonary disorders associated with an increased oxidant burden on the alveolar epithelial surface, eg, cystic fibrosis,^{14,44} ARDS,^{15,45-47} acute and chronic bronchitis,^{13,48-50} and pulmonary emphysema.^{1,3,6,10} In this regard, several lines of evidence, both *in vitro* and *in vivo*, demonstrate that other antioxidants such as SOD or catalase are able to reduce the oxidant burden in situations characterized by a dysbalance between oxidants and antioxidants in a similar fashion.^{17, 21, 22, 31, 51} Furthermore, the recent discovery that aerosol therapy with SLPI, a 12-kd serine antiprotease with 8 internal cysteine disulfide bonds, increases antineutrophil elastase capacity and ELF glutathione levels *in vivo* suggests that it may even be possible to augment both local antioxidant and antiproteolytic defenses of the respiratory epithelial surface with a single substance.^{52,53} This form of therapy is particularly well suited for lung diseases such as pulmonary emphysema which are characterized by excess of both oxidants and serine proteases on the respiratory epithelial surface.

Another promising strategy to augment the antioxidative protective screen in the lung is gene therapy to increase the expression of antioxidant genes in cells of tissues characterized by an increased oxidant burden, eg, the respiratory epithelium. In this regard, evaluation of messenger RNA from airway epithelial cells and alveolar macrophages obtained by BAL demonstrates that epithelial cells have a much lower expression of antioxidant genes.⁵⁴ Since disorders characterized by high oxidant stress typically show epithelial cell damage, and since increases in antioxidants that occur in experimental animals exposed to hyperoxia, hypoxia, cytokines, or endotoxins are most likely mediated by genetic control mechanisms,⁵⁵ transfer of genes of the antioxidant enzyme family to epithelial cells may reverse the imbalance between oxidants and antioxidants at the site of oxidant injury, and protect against cellular destruction and development of disease.⁵⁶ The transfer of a recombinant α_1 -AT gene to the lung epithelium *in vivo* to augment the antiproteolytic protection of the respiratory tract clearly demonstrates that gene therapy to enhance cellular antiproteolytic or antioxidant protection has been transformed from a purely theoretical stage to strategies that have a realistic chance of application.⁵⁷

Antioxidant therapeutic strategies show biologic efficacy and are capable of interacting favorably with both intracellular and extracellular oxidative events, resulting in a net reduction in the oxidant burden. This approach might be helpful to prevent oxidant damage to the fragile pulmonary tissue in a wide variety of respiratory diseases characterized by an imbalance between oxidants and antioxidants in the lower respiratory tract. Antioxidants, alone and in combination with antiproteases, clearly merit long-term clinical studies.

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